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Epidemiology of HIV-infection and drug resistance among tuberculosis patients in the Netherlands

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Chapter 8

Summary

Samenvatting

Dankwoord

Curriculum Vitae

This thesis comprises studies investigating to what extent global developments, such as the HIV pandemic and increasing drug resistance of *M. tuberculosis* may have an effect on the epidemiology of tuberculosis (TB) in a low prevalence area such as the Netherlands.

The HIV pandemic has had a dramatic impact on rates of TB and on TB control in populations where both infections are prevalent.

We studied the HIV prevalence among tuberculosis patients during the period 1993 through 2001 in the Netherlands. We also studied the characteristics of co-infected patients. In this study data from the national surveillance register of all patients notified with TB (all forms) was used. In addition, records or discharge notes of a random sample of 200 patients each notified in 1995 and 2001 were checked for history and result of an HIV-test. This study is described in **chapter 2**.

Over the period 1993-2001, 542 (4.1%) of all (13.269) TB patients notified in the Netherlands were reported to have HIV-infection. There has been no change in HIV prevalence among TB patients since 1993, and hereby no increase nor decrease in the impact of the HIV epidemic on TB incidences.

The highest prevalence was observed among drug users (29.2%), patients from western industrialized countries (23.1%) homeless patients (20.1%) and patients residing illegally in the country (9.1%).

There has been a change in risk group contribution over time: a significantly decreasing contribution of drug using patients as well as of patients coming from western industrialized countries (probably also a decrease in contribution of male patients having sex with men, due to improved immunity as a result of combination Anti-Retroviral Therapy (cART) and an increasing contribution of immigrants from countries with high prevalence of HIV-TB co-infection, notably Sub Saharan Africa. According to patients' records, 16% had been tested for HIV in 1995, and 21% in 2001;

18 patients tested positive (4.8%). There may be underdiagnosis of HIV-infection among TB patients, especially among these immigrants. More routine HIV-testing should be done offering HIV-testing as an integral part of the TB diagnostic process.

TB mortality increases considerably when HIV-infected, treatment of TB slows down the progression of the HIV-infection. Introduction of cART significantly reduces HIV-associated death among TB patients. In **chapter 3** the proportion of TB patients tested for HIV infection before and after introduction of cART in the Netherlands is

compared. It also describes the predictive factors for performing an HIV-test in this population. For this comparison a random sample of each 200 patients was drawn out of the data from the national surveillance register of all patients notified with TB in 1995 and 2001 respectively.

In 1995, the number of patients tested for HIV was 29 out of 184 (16%), and 39 out of 190 (21%) in 2001 ($p=0.289$). HIV tests had been done most frequently among homeless patients (71%), drug addicts (56%) and alcohol-abusing patients (60%). Significant predictive factors for HIV testing were place of residence (town), localisation of disease (pulmonary TB in combination with extrapulmonary TB) and origin (sub-Saharan Africa). Despite the introduction of cART over this period in the Netherlands the proportion of TB patients tested in 1995 and 2001 did not significantly increase. HIV testing was mainly limited to TB patients from risk groups. HIV testing should be offered to every TB patient as an integral part of the TB diagnostic process.

In **Chapter 4** the effect of HIV infection on mortality and the trend in mortality among notified TB patients in the Netherlands over the period during which cART was introduced (1993-2001) is presented. Patient data were obtained from the national surveillance register of all patients notified with TB.

HIV infection in TB patients was associated with an increased risk of death (aOR 5.71, $p < 0.002$). Age and sex-standardized mortality rates among HIV-infected TB patients decreased significantly over time, from 22.9% in 1993-1995, to 11.8 % in 1999-2001 ($p < 0.001$). No such change was observed for HIV-negative patients. The decrease in mortality is likely due to the more widespread use of cART.

Reports on associations of HIV co-infection and drug resistance among patients with TB have been contradictory. Some studies found strongly increased risks for MDR-TB among patients co-infected with TB and HIV, whereas other studies found no increased risk.

Chapter 5 reports on a population-based study of anti-TB drug resistance patterns and associations with HIV infection in the Netherlands during 1993-2001.

Patient data were obtained from the national surveillance register. Data on drug susceptibility were obtained from the National Tuberculosis Reference Laboratory. Laboratory records were matched to national surveillance register records.

In the Netherlands during 1993-2001, multidrug-resistant (MDR) TB among newly diagnosed patients was more frequent in those with HIV co-infection (5/308, 1.6%)

than in those with no HIV-infection (39/646, 0.6%; aOR 3.42, p=0.015). Four of the 5 patients co-infected with MDR-TB and HIV were foreign-born. DNA fingerprint analysis suggested that transmission had occurred outside the Netherlands. In patients who have previously been treated for TB, the possibility of rifampin resistance should be considered. Routine surveillance of resistance to anti-TB drugs will improve timely recognition of MDR TB cases and help prevent further transmission.

Chapter 6 describes demographic, clinical and microbiological features of MDR-TB patients in the Netherlands during the period 1998-2008 – it also presents factors associated with treatment outcomes, including in-vitro drug susceptibility, drug treatment and co-infections, as well as the role of surgery.

Data on drug susceptibility were obtained from the National Tuberculosis Reference Laboratory which performs drug susceptibility testing (DST) on all *M. tuberculosis* complex strains isolated from patients in the Netherlands. Retrospective data were analyzed of all charts of patients who were treated for MDR-TB either in two tertiary tuberculosis centres, hospitals or Municipal Health Services (MHSs) during the period 1 September 1998 to 1 September 2008.

During the study period, 87 patients were diagnosed with MDR-TB. 76 patients that started on treatment were evaluated for treatment outcome. Ten MDR-TB patients were HIV-co-infected (13.2%). Nine had (former) substance abuse. Seven had hepatitis B and/or C co-infection. Isolates were resistant to 5 antimycobacterial drugs on average. 64 (84.2%) had a favourable outcome (cured or completed treatment). Eight of 12 patients with an unfavourable outcome died, 6 of whom were HIV co-infected. Treatment lasted 16.9 (9-25) months on average. HIV-negative status was associated with favourable outcome (aOR 27.4, p<0.01). Eleven patients had thoracic surgery after 6.6 months of drug treatment, 2 died postoperatively due to respiratory failure.

Cases of MDR-TB in the Netherlands appear to be largely restricted to a population of immigrants from different regions of the world with a variety of co-morbidities (HIV, HBV and HCV infections, diabetes and mental conditions including drug-and alcohol addiction) and infected with multiple resistant *M. tuberculosis* strains. Nevertheless, it is possible to reach a treatment success rate of 84% for MDR-TB. HIV co-infection in MDR-TB carries an important mortality risk, and early identification of MDR-TB is therefore important in immuno-compromised patients.

Likewise is early identification of HIV co-infection essential to start ART in time, thereby improving chances of survival.

CONCLUSIONS

HIV infection has had no impact on TB prevalence in the Netherlands (probably because of the low incidences of both infections)

In contrast, **MDR TB is more prevalent among HIV-infected** TB patients, most likely because MDR TB is an imported disease and because of the HIV-infection itself.

Treatment outcomes are worse among HIV infected TB patients, as shown in chapter 4 concerning 'HIV-related mortality among tuberculosis patients in the Netherlands' and in chapter 6 concerning 'Treatment outcomes of multi-drug resistant tuberculosis in the Netherlands'

